

## REMARKS

By the foregoing amendment, the applicants have introduced an amendment to the specification as it was amended during the international phase [see "Translation Of Amendment to the Specification of Intl. Appl. No. PCT/JP99/03682 as amended under PCT Article 34 (Translation of the Annex)" submitted to the USPTO on 27 February 2001].

The foregoing amendments to the claims correct obvious errors and more clearly define the applicants' invention. Support for new claims 44-46 is found throughout the specification and claims as originally filed. No new matter is believed to have been added.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,  
MURRAY & BORUN

Thomas A. Cawley Jr.

Thomas A. Cawley, Jr., Ph.D.  
Registration No. 40,944  
6300 Sears Tower  
233 South Wacker Drive  
Chicago, IL 60606-6402  
Telephone: (312) 474-6300

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**APPENDIX A-SPECIFICATION**  
**VERSION WITH MARKINGS TO INDICATE CHANGES MADE**

*The paragraph beginning at page 11, line 17, was amended as follows.*

--The location where the nucleic acid sequence for enhancing expression of a useful gene is incorporated into a gene expression vector [is not particularly limited as long as direct or indirect enhancement of expression of a useful gene is permitted] should be the one that permit direct or indirect enhancement of expression of a useful gene by means of incorporating the nucleic acid sequence for enhancing expression of a useful gene into an expression vector which has been constructed such that the useful gene can be expressed, however, it is preferable that the location is downstream of the expression regulatory promoter sequence and upstream of the useful gene. Additionally, the nucleic acid sequence for enhancing expression of a first useful gene should be incorporated into the expression vector such that transcription and translation are carried out in the normal (i.e., from 5' to 3') direction.--

APPENDIX A-CLAIMS

VERSION WITH MARKINGS TO INDICATE CHANGES MADE

*Please amend claims 1 and 14-18 as follows.*

1. (Amended) A nucleic acid sequence for enhancing expression of a useful gene incorporated into a gene expression vector for enhancing expression of a useful gene comprising a nucleic acid sequence corresponding to a 5'-untranslated region of a viral gene or a fragment or a variant thereof, and is incorporated downstream of the expression regulatory promoter sequence and upstream of the first useful gene in a gene expression vector.

14. (Amended) The nucleic acid sequence for enhancing expression of a useful gene according to claim 12, wherein said nucleic acid sequence consists of [the following nucleotide sequence: gccagcccccc tcatgggggc gacactccac catagatcac tccctgtga ggaactactg 60 tcttcacgca gaaagcgctc agccatggcg ttagtatgag tgcgtgcag cctccaggac 120 ccccccctccc gggagagcca tagtgtctg cgaaaccggt gactacaccg gaattgccag 180 (SEQ ID NO: 1, 1-180)] nucleotides 1-180 of SEQ ID NO: 1.

15. (Amended) The nucleic acid sequence for enhancing expression of a useful gene according to claim 12, wherein said nucleic acid sequence consists of [the following nucleotide sequence: gacgaccggg tccttcttg gatcaaccccg ctcaatgcct ggagatttg gcgtgcccccc 60 gcgagactgc tagccgagta gtgtgggtc gcgaaaggcc ttgtggtaact gcctgatagg 120 gtgcctgcga gtccccggg aggtctcgta gaccgtgcac c 161 (SEQ ID NO: 1, 181-341)] nucleotides 181-341 of SEQ ID NO: 1.

16. (Amended) The nucleic acid sequence for enhancing expression of a useful gene according to claim 12, wherein said nucleic acid sequence consists of [the following nucleotide sequence:

gccagcccccc tcatgggggc gacactccac catagatcac tccctgtga ggaactactg 60 tcttcacgca gaaagcgctc agccatggcg ttagtatgag tgcgtgcag cctccaggac 120 ccccccctccc gggagagcca tagtgtctg cgaaaccggt gactacaccg gaattgccag 180 gacgaccggg tccttcttg gatcaaccccg ctcaatgcct ggagatttg gcgtgcccccc 240 gcgagactgc tagccgagta gtgtgggtc gcgaaaggcc ttgtggtaact gcctgatagg 300

gtgcttgcga gtgccccggg aggtctcgta gaccgtgcac c

341

(SEQ ID NO: 1, 1-341)] nucleotides 1-341 of SEQ ID NO:1.

17. (Amended) The nucleic acid sequence for enhancing expression of a useful gene according to claim 13, wherein said nucleic acid sequence consists of [the following nucleotide sequence:

gacgaccggg tccttcttg gatcaacccg ctcaatgcct ggagattgg gcgtcccccc 60  
gcgagactgc tagccgagta gtgtgggtc gcgaaaggcc ttgtggtaact gcctgatagg 120  
gtgcttgcga gtgccccggg aggtctcgta gaccgtgcac catgagcaca aatctaacc 180  
ctcaaagaaa aaccaaacgt aacaccaacc gccgcccaca ggacgtcaag ttcccgccg 240  
gtggtcagat cggtgggtgga gtttacctgt tgccgcgcag gggccccagg ttgggtgtgc 300  
gcgcgactag gaagacttcc gagcggtcgc aacctcgta aaggcgacaa cctatcccc 360  
aggctcgccg gcccggggc aggacctggg ctcagcccggt gtatccctgg cccctctatg 420  
gcaacgaggg catgggggtgg gcaggatggc tcctgtcgc ccgcggctcc cggcctagtt 480  
ggggcccttc ggaccccccgg cgtaggtcgc gtaatttggg taaggtcatc gat 533

(SEQ ID NO: 1, 181-713)] nucleotides 181-713 of SEQ ID NO: 1.

18. (Amended) The nucleic acid sequence for enhancing expression of a useful gene according to claim 13, wherein said nucleic acid sequence consists of [the following nucleotide sequence:

gccagcccccc tgatgggggc gacactccac catagatcac tccccctgtga ggaactactg 60  
tcttcacgca gaaagcgctc agccatggcg ttagtatgatgtgtcgacag cctccaggac 120  
ccccccctccc gggagagcca tagtggtctg cggaaaccgggt gagtacaccg gaattgccag 180  
gacgaccggg tccttcttg gatcaacccg ctcaatgcct ggagattgg gcgtcccccc 240  
gcgagactgc tagccgagta gtgtgggtc gcgaaaggcc ttgtggtaact gcctgatagg 300  
gtgcttgcga gtgccccggg aggtctcgta gaccgtgcac catgagcaca aatctaacc 360  
ctcaaagaaa aaccaaacgt aacaccaacc gccgcccaca ggacgtcaag ttcccgccg 420  
gtggtcagat cggtgggtgga gtttacctgt tgccgcgcag gggccccagg ttgggtgtgc 480  
gcgcgactag gaagacttcc gagcggtcgc aacctcgta aaggcgacaa cctatcccc 540  
aggctcgccg gcccggggc aggacctggg ctcagcccggt gtatccctgg cccctctatg 600  
gcaacgaggg catgggggtgg gcaggatggc tcctgtcgc ccgcggctcc cggcctagtt 660

ggggcccttc ggaccccccgg cgtaggctgc gtaattggg taaggtcatc gat 713

(SEQ ID NO: 1, 1-713)] nucleotides 1-713 of SEQ ID NO:1.

*Claim 19 was canceled, without prejudice.*

*Claims 21-28, 35, and 37-40 were amended as follows.*

21. (Amended) [The] A nucleic acid sequence for enhancing expression of a useful gene [according to claim 15,] wherein said nucleic acid has] incorporated into a gene expression vector for enhancing expression of a useful gene comprising a nucleic acid sequence of nucleotides 181-341 of SEQ ID NO: 1 having one thymidine inserted into position 207 of SEQ ID NO: 1, and a fragment or variant thereof.

22. (Amended) The nucleic acid sequence for enhancing expression of a useful gene according to claim 1 or claim 21, wherein said nucleic acid sequence for enhancing expression of a useful gene enhances expression of a useful gene by means of its own translation promoting activity.

23. (Amended) The nucleic acid sequence for enhancing expression of a useful gene according to claim 1 or claim 21, wherein said nucleic acid sequence for enhancing expression of a useful gene enhances expression of a useful gene by means of accelerating IRES activity.

24. (Amended) A nucleic acid sequence for enhancing expression of a useful gene comprising [the following] a nucleotide sequence[:

gccagccccc tcatgggggc gacactccac catagatcac tccccgtgta ggaactactg 60

tcttcacgca gaaagcgctc agccatggcg ttagtatgag tgcgtgcag cctccaggcc 120

ccccctccc gggagagcca tagtggctg cggAACCGGT gagtacaccg gaattgccag 180

gacgaccggg tccttcttg gatcaatccc gctcaatgcc tggagatttg ggcgtcccc 240

cgcgagactg ctagccgagt agtgttgggt cgcgaaaggc cttgtggta tgcctgatag 300

ggtgcttgcg agtgccccgg gaggtctcgt agaccgtgca cc 342

(SEQ ID NO: 7)] of SEQ ID NO: 7, which enhances expression of a useful gene by means of

promoting mRNA translation in an IRES-dependent manner.

25. (Amended) A nucleic acid sequence for enhancing expression of a useful gene which comprises a polynucleotide having a similar IRES activity to an IRES activity of [the following] a nucleotide sequence[:

gccagcccccc tcatgggggc gacactccac catagatcac tcccctgtga ggaactactg 60  
tcttcacgca gaaagcgctc agccatggcg ttagtatgag tgcgtgcag cctccaggcc 120  
ccccctccc gggagagcca tagtgtctg cggaaccgggt gagtacaccg gaattgccag 180  
gacgaccggg tcctttcttg gatcaatccc gctcaatgcc tggagatttgcgtgcccc 240  
cgcgagactg ctagccgagt agtgtgggt cgccgaaaggc cttgtgtac tgcctgatag 300  
ggtgcttgcg agtgccccgg gaggctctcg agaccgtgca cc 342

(SEQ ID NO: 7)] of SEQ ID NO: 7, and consisting of a fragment or a variant of the sequence, which enhances expression of a useful gene by means of promoting mRNA translation in an IRES-dependent manner.

26. (Amended) An isolated polynucleotide consisting of [the following] a nucleotide sequence[:

gccagcccccc tcatgggggc gacactccac catagatcac tcccctgtga ggaactactg 60  
tcttcacgca gaaagcgctc agccatggcg ttagtatgag tgcgtgcag cctccaggcc 120  
ccccctccc gggagagcca tagtgtctg cggaaccgggt gagtacaccg gaattgccag 180  
gacgaccggg tcctttcttg gatcaatccc gctcaatgcc tggagatttgcgtgcccc 240  
cgcgagactg ctagccgagt agtgtgggt cgccgaaaggc cttgtgtac tgcctgatag 300  
ggtgcttgcg agtgccccgg gaggctctcg agaccgtgca cc 342

(SEQ ID NO. 7)] of SEQ ID NO:7.

27. (Amended) An isolated polynucleotide having a similar IRES activity to an IRES activity of [the following] a nucleotide sequence[:

gccagcccccc tcatgggggc gacactccac catagatcac tcccctgtga ggaactactg 60  
tcttcacgca gaaagcgctc agccatggcg ttagtatgag tgcgtgcag cctccaggcc 120  
ccccctccc gggagagcca tagtgtctg cggaaccgggt gagtacaccg gaattgccag 180  
gacgaccggg tcctttcttg gatcaatccc gctcaatgcc tggagatttgcgtgcccc 240

cgcgagactg ctagccgagt agtgtgggt cgcgaaaggc cttgtggtag tgcctgatag 300

ggtgcttgcg agtgcccccgg gaggctcgat agaccgtgca cc 342

(SEQ ID NO: 7)], of SEQ ID NO: 7 and consisting of a fragment or a variant of said sequence.

28. (Amended) A gene expression vector comprising the nucleic acid sequence for enhancing expression of a useful gene according to claim 1 or claim 21.

35. (Amended) A therapeutic composition for treating diseases resulting from reduction of cap-dependent mRNA translation in a body of organisms, comprising the nucleic acid sequence for enhancing expression of a useful gene according to claim 1 or claim 21 such that translation of mRNA can be promoted by means of introducing said nucleic acid sequence for enhancing expression of a useful gene into the body of the organisms.

37. (Amended) A method for determining the severity of hepatitis C, comprising the steps of: detecting the presence of a target polynucleotide sequence contained in a biological sample derived from a test subject, by using the polynucleotide according to claim 26 or claim 27 as the target; and determining the severity of the hepatitis C based on the presence of the sequence.

38. (Amended) The nucleic acid sequence for enhancing expression of a useful gene according to claim [16, wherein said nucleic acid has] 21 further comprising a nucleic acid sequence of nucleotides 1-180 of SEQ ID NO: 1 having one thymidine inserted into position 207 of SEQ ID NO: 1, and a fragment or variant thereof.

39. (Amended) The nucleic acid sequence for enhancing expression of a useful gene according to claim [17, wherein said nucleic acid has] 21 further comprising a nucleic acid of nucleotides 342-713 of SEQ ID NO: 1 having one thymidine inserted into position 207 of SEQ ID NO: 1, and a fragment or variant thereof.

40. (Amended) The nucleic acid sequence for enhancing expression of a useful gene according to claim [18, wherein said nucleic acid has] 21 further comprising a nucleic acid sequence of nucleotides 1-180 and 342-713 of SEQ ID NO: 1 having one thymidine inserted into position 207 of SEQ ID NO: 1, and a fragment or variant thereof.

*New claims 44-46 were added herein.*

44. The nucleic acid sequence for enhancing expression of a useful gene according to claim 1, wherein the 5'-untranslated region comprises a sequence corresponding to at least one region selected from the group consisting of a pyrimidine-rich tract, BoxA, BoxB, a trans factor-binding site, and a combination thereof.

45. The nucleic acid sequence for enhancing expression of a useful gene according to claim 44, wherein said nucleic acid comprises a sequence having substitution, deletion, insertion and/or addition of a single or a few nucleotides of a sequence derived from a wild-type virus within the sequence or a proximate sequence in at least one position corresponding to a pyrimidine-rich tract, BoxA, BoxB and/or trans factor-binding site contained in the 5'-untranslated region.

46. A therapeutic composition for treating diseases resulting from reduction of IRES activity in a body of organisms, comprising the nucleic acid sequence for enhancing expression of a useful gene according to claim 25 such that translation of mRNA can be promoted by means of introducing said nucleic acid sequence for enhancing expression of a useful gene into the body of the organisms.